BioMarin Announces New and Updated Data at 2021 American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meeting Demonstrating Commitment to Understanding Achondroplasia and Potential Treatment Choice

Normal Progression of Bone Age with Chronological Age Over 60 Months with Vosoritide for Children with Achondroplasia

Vosoritide Well-Tolerated, Safety Profile Unchanged

Data on Quality of Life, Natural History, and Caregiver Experience Provide Additional Insights into Lifetime Impact of Achondroplasia

SAN RAFAEL, Calif., April 15, 2021 /PRNewswire/ -- BioMarin Pharmaceutical Inc. (NASDAQ: BMRN) presented new and updated data at the 2021 American College of Medical Genetics and Genomics (ACMG) Annual Clinical Genetics Meeting that demonstrates the Company's ongoing commitment to understanding the lifetime impact of achondroplasia and the potential of an investigational treatment choice to address the root cause of achondroplasia.

The Company provided an update on its investigational treatment, vosoritide, an analog of C-type Natriuretic Peptide (CNP) in children with achondroplasia, the most common form of disproportionate short stature in humans. An ongoing, open-label, Phase 2 extension study of vosoritide for achondroplasia showed that improvement in growth velocity is sustained over 5 years of treatment and does not reduce the total duration of the growth period. Bone age progressed normally and posterior-anterior (PA) X-rays of the hand annually showed no significant changes in bone mineral content or bone mineral density.

The mean (±SD) increase in AGV observed over 60 months of treatment was 1.35 (±1.07) cm/year. There was an overall mean (±SD) increase in height Z-score (which measures the height deficit in standard deviations relative to the mean for age and gender-matched average stature children) at 60 months of 0.78 (±0.70) using the CDC standards for average stature children. Vosoritide was well tolerated at the doses of 15 and 30 µg/kg/day, and the safety profile remained unchanged with no new types of adverse events (AEs) developing over time, and no serious AEs were related to therapy.

"We are encouraged by the new data emerging from this extension study indicating that after five years of treatment, bone age is not accelerated and the total duration of the growth period is not shortened," said Paul Harmatz, M.D., Professor in Pediatrics with a focus on skeletal dysplasias at UCSF Benioff Children's Hospital in Oakland, California and clinical investigator in the vosoritide clinical program. "While still early, we're seeing that proportionality is not worsening. We look forward to further follow up over time in the extension study for additional insights on proportionality."

"It is important to understand the impact of achondroplasia on those affected and their caregivers in order to develop a therapeutic choice for families that has the potential to alter the course of achondroplasia in a way that is considered meaningful by families and treating physicians," said Hank Fuchs, M.D., President Worldwide Research and Development. "We are committed to understanding the potential lifetime impact of

achondroplasia and providing information to support those interested in potential therapeutic options. We are grateful to the families and study investigators whose involvement is essential to exchanging scientific and clinical information to advance the standard of care in achondroplasia."

"We believe it is critical for families with achondroplasia to be supported and have access to the resources they need for their children. We applaud BioMarin for its efforts to contribute to the body of scientific knowledge to understand the lifetime impact of achondroplasia and the potential ways to address unmet needs that may result," said Mary Andrews, Chief Executive Officer of The Magic Foundation. "We are supportive of BioMarin's research efforts to address the scientific gaps on the impact of achondroplasia, as well as its robust clinical program for a potential treatment option for any family that seeks it."

In addition to the Phase 2 extension study, BioMarin also presented an oral presentation and a poster on its multinational observational study, Lifetime Impact of Achondroplasia in Europe (LIASE), the first multinational, observational, and retrospective natural history study of achondroplasia conducted across Europe, with a cross-sectional patient reported outcome (PRO) component collected at enrollment across several quality of life (QoL) domains using standardized tools. This study collected retrospective medical data for at least five years prior to enrollment with the goal of quantifying the impact of achondroplasia across the age spectrum by measuring the clinical burden, healthcare resource use, and health-related quality of life (HRQoL) of affected individuals. The study results showed that people with achondroplasia experience an increase in medical conditions and comorbidities, surgical burden, and hospital visits across the age spectrum with the most notable impact in the youngest and oldest age groups. Additionally, an exploratory analysis showed correlations between height and height Z-score, and comorbidities, such as ear, nose, and throat (ENT) issues, and spinal cord compression/stenosis. The poster presented from this study further highlights that across several questionnaires, HRQoL scores were lower than the general population, especially in physical and psychosocial domains, and describes a correlation between height, height Z-score, and HRQoL. These findings underscore the need for people with achondroplasia to be assessed clinically throughout their lifetime and a need for developing consensus-based management guidelines.

Additional studies presented at the medical meeting include the following:

Achondroplasia Caregiver Survey- A global perspective on diagnostic pathways, healthcare management and personal impact from the caregivers of children with achondroplasia

This global study surveyed 660 caregivers of children with achondroplasia in seven countries (Argentina, Brazil, Colombia, France, Spain, Italy, and Japan) and the results suggest that achondroplasia management can be complex, requiring coordination among numerous healthcare specialties, and that there is substantial healthcare resource use among children with achondroplasia.

Experience of individuals with achondroplasia and their caregivers: interim results from qualitative studies

This poster presentation describes the results from two qualitative studies. One study examined the impact of achondroplasia on the lives of affected individuals and caregivers in the US and Spain and found that many individuals with achondroplasia and their caregivers experience daily challenges requiring adaptations related

to achondroplasia. Individuals and caregivers also reported some positive aspects of living with achondroplasia. Another study explores perceptions of meaningful outcomes in achondroplasia in light of emerging precision therapies. The interim findings suggest that treatment goals include the reduction of medical complications, and improvements in daily function and psychosocial well-being.

Description of Phase 2 Dose Finding Study

The primary objectives of the open-label, sequential cohort, dose-finding study were to evaluate the safety and tolerability of daily subcutaneous vosoritide and to determine the dose to carry forward to Phase 3. Secondary objectives were to evaluate the effects of vosoritide on change from pre-treatment baseline in annualized growth velocity (cm/year), height Z-scores, and body segment proportionality, the vosoritide pharmacokinetic (PK) profile, and biomarkers of vosoritide activity, and endochondral ossification.

Vosoritide Safety

Vosoritide, administered in approximately 38,000 injections, was generally well tolerated at all doses. The majority of adverse events (AEs) were mild and no serious adverse events (SAEs) were reported as study drug related. Across all doses, injection site reactions and hypotension were the most common drug-related AEs. All injection site reaction events were transient. AEs of hypotension were mild, transient and resolved without medical intervention, and the majority were asymptomatic and reported in context of routine blood pressure measurements. No new safety findings were observed. There were no AEs related to disproportionate bone growth or bone pathology. There has been no evidence of accelerated bone age (as assessed by radiologists blinded to the age of the subjects) or negative changes in bone mineral density.

Regulatory Status

In 2020, the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) accepted and validated the marketing authorization application for vosoritide for achondroplasia. The Committee for Medicinal Products for Human Use (CHMP) opinion is expected in Europe in June of 2021. The U.S. New Drug Application (NDA) for vosoritide is under review by the FDA with a Prescription Drug User Fee Act (PDUFA) target action date of August 20, 2021. In the United States, the Company has chosen to provide the two-year outcomes from the Phase 3 extension study to the FDA as additional data to convey the vosoritide treatment effect and long-term durability. The Company believes that supplying this additional data could result in a major amendment, resetting the current PDUFA target action date out three months to November.

In January 2021, the Company received notice from the FDA that the NDA for vosoritide had been granted Priority Review Designation based on the serious pediatric indication it addresses, and the lack of treatment options currently available. Consistent with FDA's policy on changes to review classification for an ongoing application review, the PDUFA action date is not affected by this designation. If approved, the vosoritide NDA may qualify for a Priority Review Voucher (PRV). A PRV confers priority review to a subsequent drug application that would not otherwise qualify for that designation. The rare pediatric disease review voucher program is designed to encourage development of new drugs and biologics for the prevention or treatment of rare pediatric diseases.

Upon the acceptance of the regulatory submission for vosoritide, the Agency reiterated a position raised during the Pediatric Advisory Committee (PAC) and Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) held on May 11, 2018 recommending two-year controlled trials in different age groups. BioMarin believes the highly persuasive outcomes from the one-year randomized, double-blind, placebo-controlled Phase 3 trial, coupled with data from the Phase 2 program with up to five years of long-term follow-up that has been compared to robust natural history data on growth and the updated two-year data from the Phase 3 study, offers a rigorous and reliable method to assess whether vosoritide has a durable impact on the rate of endochondral bone growth that ultimately increases final adult height.

Vosoritide has also received orphan drug designation from the FDA and EMA for the treatment of children with achondroplasia. The Orphan Drug Designation program is intended to advance the evaluation and development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases or conditions.

Listing of BioMarin Presentations on Achondroplasia

Title	**Author(s)**	**Author Affiliation**
Platform Presentation: *Lifetime impact of achondroplasia in Europe (LIAISE): findings from a multinational observational study*	Mohamad Maghnie, MD, PhD	Department of Pediatrics, IRCCS Instituto Giannina Gaslini, Genova, Italy
Poster: *Vosoritide for Children with Achondroplasia: A 60-month Update from an Ongoing Phase 2 Clinical Trial*	Julie Hoover-Fong[1],Melita Irving[2], Carlos Bacino[3], Joel Charrow[4], Valerie Cormier-Daire[5], Lynda Polgreen[6], Patricia Dickson[7], Paul Harmatz[8], Kevin Larimore[9], Kala Jayaram[9], Alice Huntsman Labed[9], Elena Fisheleva[9], George Jeha[9], Jonathan Day[9], John Phillips[10], Ravi Savarirayan[11]	[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA [2]Guy's and St. Thomas' NHS Foundation Trust, Evelina Children's Hospital, London, UK [3]Baylor College of Medicine, Houston, TX, USA

		[4]Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, [5]Institut Imagine, Université Paris Descartes, Hôpital Necker - Enfants Malades, Paris, France [6]The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA, USA [7]Washington University School of Medicine, St. Louis, MO [8]UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA [9]BioMarin Pharmaceutical Inc., Novato, CA, USA [10]Vanderbilt University Medical Center, Nashville, TN, USA [11]Murdoch Children's Research Institute, Royal Children's Hospital Victoria, University of Melbourne, Parkville, Victoria, Australia
Poster: *Lifetime impact of achondroplasia in Europe (LIAISE): findings from a multinational observational*	Mohamad Maghnie[1], Oliver Semler[2], Encarna Guillen-Navarro[3], Awi Wiesel[4], Anna Elsa Maria Allegri[1], Angelo Selicorni[5], Antonio Gonzalez-Meneses[6], Karen Heath[7], Giuseppe Zampino[8], Gabriele Haeusler[9], Lars Hagenäs[10], Antonio Leiva-Gea[11], Vanesa López González[12], Adalbert Raimann[9], Fernando Santos Simarro[7], Silvia Tajè[13], Diana-Alexandra Ertl[9], Pernille	[1]Department of Pediatrics, IRCCS Istituto Giannina Gaslini, Genova, Italy [2]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Pediatrics, Cologne,

study	Axél Gregersen[14], Jeanne Pimenta[15], Shelda Cohen[15], James Jarrett[15], Richard Rowell[16], Renée Shediac[16], Swati Mukherjee[15], Klaus Mohnike[17]	Germany [3] Hospital Clínico Universitario Virgen de la Arrixaca. Universidad de Murcia: El Palmar, Murcia, Spain [4,]UNIVERSITÄTSMEDIZIN der Johannes Gutenberg-Universität Mainz [5] UOC Pediatria, Como, Italy [6]Unidad de Dismorfología y metabolism Hospital Universitario Virgen del Rocío, Sevilla Spain [7,]Hospital Universitario La Paz [8]IRCCS Fondazione Policlinico Universitario A. Gemelli – Rome [9]Universitätsklinik für Kinder und Jugendheilkunde, Medizinische Universität Wien, Vienna, Austria [10]Karolinska University Hospital, Stockholm, Sweden [11,]Hospital Universitario Virgen de la Victoria, Málaga, Spain [12]Sección de Genética Médica - Servicio de Pediatría Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain

		[13]Società Italiana Malattie Genetiche Pediatriche e Disabilità (SIMGePed), Milan, Italy [14]Klinisk Genetisk Afdeling, Aarhus Universitetshospital, Aarhus N, Denmark [15]BioMarin Europe, London, UK [16]BioMarin Pharmaceutical Inc., Novato, CA, USA [17] Otto-von-Guericke Universität, Universitätskinderklinik Madgdeburg, Germany Otto-von-Guericke Universität, Universitätskinderklinik Madgdeburg, Germany
Poster: *Health-related quality of life (HRQoL) in achondroplasia: findings from a multinational, observational study*	Mohamad Maghnie[1], Oliver Semler[2], Encarna Guillen-Navarro[3], Awi Wiesel[4], Anna Elsa Maria Allegri[1], Angelo Selicorni[5], Antonio Gonzalez-Meneses[6], Karen Heath[7], Giuseppe Zampino[8], Gabriele Haeusler [9], Lars Hagenäs[10], Antonio Leiva-Gea[11], Vanesa López González[12], Adalbert Raimann[9], Fernando Santos Simarro[7], Silvia Tajè[13], Diana-Alexandra Ertl[9], Pernille Axél Gregersen[14], Erik Landfeldt[15], Luiz Causin[16], James Jarrett[16], Jennifer Quinn[16], Renée Shediac[17], Swati Mukherjee[16], Klaus Mohnike[18]	[1]Department of Pediatrics, IRCCS Istituto Giannina Gaslini, Genova, Italy [2]University of Cologne, Faculty of Medicine and University Hospital Cologne, Department of Pediatrics, Cologne, Germany [3] Hospital Clínico Universitario Virgen de la Arrixaca. Universidad de Murcia: El Palmar, Murcia, Spain [4] UNIVERSITÄTSMEDIZIN der Johannes Gutenberg-

		Universität Mainz [5]UOC Pediatria, Como, Italy [6]Unidad de Dismorfología y metabolism Hospital Universitario Virgen del Rocío, Sevilla Spain [7]Hospital Universitario La Paz [8]IRCCS Fondazione Policlinico Universitario A. Gemelli – Rome [9]Universitätsklinik für Kinder und Jugendheilkunde, Medizinische Universität Wien, Vienna, Austria [10]Karolinska University Hospital, Stockholm, Sweden [11]Hospital Universitario Virgen de la Victoria, Málaga, Spain [12]Sección de Genética Médica - Servicio de Pediatría Hospital Clínico Universitario Virgen de la Arrixaca, Murcia, Spain [13]Società Italiana Malattie Genetiche Pediatriche e Disabilità (SIMGePed), Milan, Italy [14]Klinisk Genetisk Afdeling, Aarhus Universitetshospital, Aarhus N, Denmark

		[15]ICON plc, Stockholm, Sweden [16]BioMarin Europe, London, UK [17]BioMarin Pharmaceutical Inc., Novato, CA, USA [18] Otto-von-Guericke Universität, Universitätskinderklinik Madgdeburg, Germany Otto-von-Guericke Universität, Universitätskinderklinik Madgdeburg, Germany
Poster: *Experiences of individuals with achondroplasia and their caregivers: interim results from qualitative studies*	Renée Shediac, PhD[1], Olga Moshkovich, MPH[2], Hannah Lewis, PhD[2], Rachel Ballinger, PhD[2], Sarah McGraw, PhD[4] Jeffrey C. Henne, MA[4] Jennifer Quinn[5], Er Chen[1], Adelpha Abrahamson Larkin[1], Dominique Kelly[1]	[1]BioMarin Pharmaceutical Inc., Novato, CA, USA [2]ICON, Patient Centred Outcomes, San Francisco, CA USA [3]ICON, Patient Centred Outcomes, London, UK [4]The Henne Group, San Francisco, CA [5]BioMarin Europe, London, UK [1]BioMarin Pharmaceutical Inc., Novato, CA, USA
Poster: *Achondroplasia Caregiver Survey – A global perspective on diagnostic pathways,*	Wagner Baratela[1], Inês Alves[2], Wayne Pan[3], Jeanne M Pimenta[3], Charlotte Roberts[3], Marco Sessa[4], Susana Noval Iruretagoyena[5], Nakamura A[6], Niiyama N[7]	[1]Hospital Sirio-Libanes, Sao Paolo, Brazil; [2]ANDO Portugal / ERN BOND, Evora, Portugal; [3]BioMarin Pharmaceutical Inc

healthcare management and personal impact from carers of children with Achondroplasia		[4]AISAC, Milan, Italy; [5]ALPE, Gijón, Spain [6]Tsukushinbo, Kita, Sakai, Osaka Prefecture, Japan [7]Tsukushinokai, Matsuyama, Ehime Prefecture, Japan

About Achondroplasia

Achondroplasia, the most common form of skeletal dysplasia leading to disproportionate short stature in humans, is characterized by slowing of endochondral ossification, which results in disproportionate short stature and disordered architecture in the long bones, spine, face and base of the skull. This condition is caused by a change in the fibroblast growth factor receptor 3 gene (FGFR3), a negative regulator of bone growth. Beyond disproportionate short stature, people with achondroplasia can experience serious health complications, including foramen magnum compression, sleep apnea, bowed legs, mid-face hypoplasia, permanent sway of the lower back, spinal stenosis and recurrent ear infections. Some of these complications can result in the need for invasive surgeries such as spinal cord decompression and straightening of bowed legs. In addition, studies show increased mortality at every age.

More than 80% of children with achondroplasia have parents of average stature and have the condition as the result of a spontaneous gene mutation. The worldwide incidence rate of achondroplasia is about one in 25,000 live births. Vosoritide is being tested in children whose growth plates are still "open", typically those under 18 years of age. This is approximately 25% of people with achondroplasia. In the U.S., Europe, Latin America, the Middle East, and most of Asia Pacific, there are currently no licensed medicines for achondroplasia.

About BioMarin

BioMarin is a global biotechnology company that develops and commercializes innovative therapies for patients with serious and life-threatening rare and ultra-rare genetic diseases. The company's portfolio consists of six commercialized products and multiple clinical and pre-clinical product candidates. For additional information, please visit www.biomarin.com. Information on such website is not incorporated by reference into this press release.

Forward-Looking Statement

This press release contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc. (BioMarin), including, without limitation, statements about: the development of BioMarin's

vosoritide program generally; the potential benefits of vosoritide; the continued clinical development of vosoritide and the timing and conduct of such clinical program; the possible results of such studies; the timing of actions by regulatory authorities including the expectation of the CHMP opinion for vosoritide in Europe in June of 2021; the potential for the vosoritide NDA, if approved, to qualify for a Priority Review Voucher; and the plan to submit the second year of Phase 3 data to the FDA and the potential that this could result in a major amendment, resetting the current PDUFA date out three months to November. These forward-looking statements are predictions and involve risks and uncertainties such that actual results may differ materially from these statements. These risks and uncertainties include, among others: results and timing of current and planned preclinical studies and clinical trials of vosoritide; our ability to enroll participants into such clinical trials, our ability to successfully manufacture vosoritide; the content and timing of decisions by the U.S. Food and Drug Administration, the European Commission and other regulatory authorities concerning vosoritide; and those other risks and uncertainties detailed from time to time under the caption "Risk Factors" and elsewhere in the BioMarin's Securities and Exchange Commission (SEC) filings, including, without limitation, BioMarin's Annual Report on Form 10-K for the year ended December 31, 2020, and future SEC filings and reports by BioMarin. BioMarin undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information, future events or changes in its expectations.

Contacts:

Investors	Media
Traci McCarty	*Debra Charlesworth*
BioMarin Pharmaceutical Inc.	*BioMarin Pharmaceutical Inc.*
(415) 455-7558	*(415) 455-7451*

SOURCE BioMarin Pharmaceutical Inc.
